REMARKS

I. STATUS OF THE CLAIMS.

Claims 88-104 and 122-138 are presently pending, with claims 103-104 and 122-126 indicated as being withdrawn. Claims 1-87 and 105-121 were previously canceled without prejudice to subsequent revival, including in a continuation or divisional application. Claims 88 and 90-92 have been amended; all of these amendments are fully supported by the application as filed and introduce no new matter. Claims 88 has been amended to specify a recombinant polypeptide comprising the polypeptide sequence of SEQ ID NO:56. Claim 90 has been amended to specify the term "polyethylene glycol" for the abbreviation "PEG". Claim 91 has been amended to specify the polypeptide of claim 90, wherein one PEG molecule is covalently attached to the polypeptide. Claim 92 has been amended to specify the term "kiloDalton" for the abbreviation "kDa".

New claims 122-138, which have been added, are fully supported by the specification as filed and do not introduce any new matter. Support for claim 122 is provided throughout the specification, including at, but not limited to, e.g., page 71, lines 4-11. Support for claim 123 is provided throughout the specification, including at, but not limited to, e.g., page 34, lines 20-28. Support for claim 124 is provided throughout the specification, including at, but not limited to, e.g., page 53, lines 8-12. Support for claim 125 is provided throughout the specification, including at, but not limited to, e.g., page 80, line 7 to page 82, line 18. Support for claims 126-128 is provided throughout the specification, including at, but not limited to, e.g., page 80, line 1 to page 81, line 31. Support for claims 129-132 is provided throughout the specification, including at, but not limited to, e.g., page 80, lines 1-31. Support for claims 133-135 is provided throughout the specification, including at, but not limited to, e.g., page 80, lines 1-23. Support for claims 136-138 is provided throughout the specification, including at, but not limited to, e.g., page 81, lines 5-23.

II. STATUS OF INFORMATION DISCLOSURE STATEMENTS.

Applicants thank the Examiner for his review of certain previously submitted Information Disclosure Statement submitted. However, one Information Disclosure Statement submitted on

July 27, 2006 has not yet been considered. This Information Disclosure Statement, which was a copy of an Information Disclosure Statement submitted in parent application USSN 10/084,706, included a Form PTO/SB/08A-B listing three foreign patent documents and one non-patent literature document (O'Connell et al., "The Influence of Flanking Sequences on O-Glycosylation," *Biochemical and Biophysical Research Communications*, 180(2):1024-1030 (1991)). Applicants respectfully request that the information cited in this Information Disclosure Statement be considered in the instant application and that the Examiner return to Applicant the submitted Form PTO/SB/08A-B with his initials confirming consideration of the cited information.

III. REQUEST FOR ACKNOWLEDGEMENT OF SUBMISSION OF CERTIFIED COPY OF DANISH PRIORITY APPLICATION IN RELATED APPLICATION.

A certified copy of Danish Patent Application No. PA 2001 00333, which was filed in the Danish Patent Office on March 1, 2001 and to which the instant application claims priority under 35 USC § 119, was submitted in parent application USSN 10/084,706 (now U.S. Patent No. 7,144,574) on November 8, 2002. Applicants respectfully request that the Examiner acknowledge and verify the priority claim to Danish Patent Application No. PA 2000 00333 in the instant application in the next Office Action Summary (Form PTOL-326).

IV. REQUEST FOR REJOINDER PURSUANT TO MPEP § 821.04.

MPEP § 821.04 provides for rejoinder of process claims that depend from or otherwise incorporate all of the limitations of product claims, once such product claims are found allowable. Applicants request that claims 103-104 and 125-138 (drawn to methods of treating a mammal) be rejoined upon a finding of allowability of the product claims from which they depend.

V. OBJECTIONS TO THE SPECIFICATION AND AMENDMENTS TO THE SPECIFICATION.

The Examiner requests that the specification be amended to update the priority information. Office Action, page 2. The specification was amended to specify the priority information in the Preliminary Amendment filed by Applicants on June 27, 2003. Parent

application USSN 10/084,706 has now issued as U.S. Patent No. 7,144,574. Applicants have amended the instant specification to include this issued patent number.

The Examiner noted the "use of the trademark Betaseron, Avonex and Rebit [sic]" in the application and stated that such terms should be capitalized and accompanied by the appropriate generic terminology. *Id.* Applicants thank the Examiner for his detailed review of the specification. The specification has been amended to include the appropriate generic terms for each such trademark.

The Examiner appears to object to the specification due to the use of the abbreviation "IFNB" for "interferon β" and suggests that the abbreviation "IFN-β" be replaced with abbreviation "IFNB" throughout the specification. However, Applicants note that the specification explicitly indicates at page 10, lines 19-20 that the abbreviations "IFNB" and "IFN-β" are used interchangeably with "interferon β". Thus, Applicants believe that the use of the abbreviation in the specification "IFNB" is clear and no amendment of the specification is necessary. Withdrawal of this objection to the specification is respectfully requested.

The specification has also been amended to correct several inadvertent typographical errors.

VI. OBJECTION TO THE DRAWINGS.

The Examiner appears to object to Figure 2, stating that the Y-axis of Figure 2 provides no information with respect to what is being measured. This objection is respectfully traversed. As indicated in the specification at page 10, line 12, Figure 2 illustrates the antiviral activity of a conjugate of the invention. In Figure 2, the Y-axis of the graph is clearly labeled with the term "OD450" (i.e., optical density at 450 nm), and the specification discloses that antiviral activity of a polypeptide or conjugate of the invention can be assessed by an assay involving measurement of absorbance at 450 nm. See the specification, including at, but no limited to, e.g., page 86, line 31 to page 87, line 16. Thus, Figure 2 plainly indicates what is being measured. Withdrawal of this objection is respectfully requested.

VII. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS.

Claims 88-95 and 102 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 5-11, and 14-24 of U.S. Patent No. 6,531,122 [hereinafter "the '122 patent"] in view of U.S. Patent No. 7,144,574 [hereinafter "the '574 patent"]. Office Action, page 3. The Examiner takes the position that:

> The instant invention is drawn to IFN-β variant, a method of making the variant polypeptide and a method of treatment.
>
> Pederson et al. (U.S. Patent No. 6,531,122) disclose IFN-β variants exhibiting IFN-β activity, comprising a variant sequence, which differs from the wild type human IFN-β sequence SEQ ID NO:2 in no more than 15 amino acid residues. However, the claims do not specifically recite IFN-β variant of SEQ ID NO:56 that has the following amino acids changed in SEQ ID NO:2 (C17S,Q49N, Q51N, D100F [sic], F111N and R113T). The claims also do not recite the molecular weight of PEG.
>
> Rasmussen et al. (U.S. Patent No. 7,144,574) disclose changes C17S and D110F of SEQ ID NO:2 (see claims 17 and 19). In addition, Rasmussen also discloses the molecular weight of the PEG (column 17). Therefore, it would have been *prima facie* obvious at the time of the invention to generate PEGylated IFN-β variants with specific amino acid changes because Rasmussen et al. reference discloses the specific amino acid changes and covalently attached a PEG molecule. One of ordinary skill in the art would have been motivated to generate PEGylated proteins because of the stability of the protein. Thus, IFN-β variant of SEQ ID NO:56 is an obvious embodiment of Pedersen et al. Therefore, the instant invention is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, and 14-24 of Pedersen et al. (U.S. Patent No. 6,531,122) in view of Rasmussen et al (U.S. Patent No. 7,144,574).

Id. at page 4.

This rejection is respectfully traversed as follows.

The doctrine of obviousness-type double patenting is a judicially created doctrine designed to prevent improper extension of patent rights by prohibiting the issuance of claims in a second patent that are directed to subject matter that is not patentably distinct from the subject matter of the claims in the prior first patent. To establish a *prima facie* case of obviousness-type double-patenting of a claim pending in a later patent application, such claim must be shown to be patentably indistinct from a claim in an earlier issued patent. The claim of the earlier issued patent must be applied alone or as a primary reference in combination with the prior art to demonstrate the unpatentability of the claim in the later application. There must be clear

evidence to establish why the subject matter of a claim in the second later application would have been obvious over the subject matter of a claim in the first issued patent.

Applicants respectfully submit that a proper *prima face* case of obviousness-type double-patenting over the '122 patent has not been established for any of pending claims 88-95 and 102. First, Applicants note that the '574 patent issued based on U.S. Application Serial No. 10/084,706, filed February 26, 2002. USSN 10/084,706 is the parent application of the instant application 10/609,296. Thus, the '574 patent is not prior art to the instant application. Consequently, the teachings of the '574 patent cannot be used to support an obviousness-type double patenting rejection that any of the instant claims is an obvious variation of any claim of the '122 patent.

Second, Applicants respectfully submit that the Examiner has not shown that claim 88 or any of claims 89-95 or 102 dependent thereon constitutes an obvious variation of any claim of the '122 patent. Claim 88 specifies a recombinant polypeptide comprising the polypeptide sequence of SEQ ID NO:56. The polypeptide sequence of SEQ ID NO:56 includes the following six amino acid substitutions relative to the human IFN-β sequence shown in SEQ ID NO:2 – C17S+Q49N+Q51T+D110F+F111N+R113T. As the Examiner expressly admits, none of the claims of the '122 patent recites or suggests the specific polypeptide sequence set forth in SEQ ID NO:56. Applicants respectfully submit that the Examiner cannot show that claim 88 or any pending claim dependent thereon is merely an obvious variation of any claim of the '122 patent. For at least these reasons, Applicants believe the rejection is entirely improper and respectfully request that it be withdrawn.

Claims 88-95 and 102-104 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 5-12, 15-21, 23-25, and 27-32 of U.S. Patent No. 7,238,344 [hereinafter "the '344 patent"] in view of the '574 patent. Office Action, pages 4-5. In support of this rejection, the Examiner states:

> Pedersen et al. (U.S. Patent No. 7,238, 344) disclose IFN-β variants exhibiting IFN-β activity, comprising a variant sequence, which differs from the wild type human IFN-β sequence SEQ ID NO:2 in no more than 8 amino acid residues. However, the claims do not specifically recite IFN-β variant of SEQ ID NO:56 that has the following amino acids changed in SEQ ID NO:2 (C17S,Q49N, Q51N, D100F [sic], F111N and R113T). The claims also do not recite the molecular weight of PEG.

> Rasmussen et al. (U.S. Patent No. 7,144,574) disclose changes D110F of SEQ ID NO:2 (see claims 17 and 19). In addition, Rasmussen also discloses the molecular weight of the PEG (column 17). Therefore, it would have been *prima facie* obvious at the time of the invention to generate PEGylated IFN-β variants with specific amino acid changes because Rasmussen et al. reference discloses the specific amino acid changes and covalently attached a PEG molecule. One of ordinary skill in the art would have been motivated to generate PEGylated proteins because of the stability of the protein. Thus, IFN-β variant of SEQ ID NO:56 is an obvious embodiment of Pedersen et al. Therefore, the instant invention is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 5-12, 15-21, 23-25 and 27-32 of Pedersen et al. (U.S. Patent No. 7,238,344) in view of Rasmussen et al (U.S. Patent No. 7,144,574).

Id. at page 5.

This rejection is respectfully traversed. As explained above, the '574 patent issued based on USSN 10/084,706, which is the parent application of the instant application. Therefore, the '574 patent is not prior art to the instant application and the teachings of the '574 patent cannot be used to support an obviousness-type double patenting rejection that any of the instant claims is an obvious variation of any claim of the '344 patent.

Furthermore, the Examiner has not shown – and Applicants respectfully submit cannot show – that claim 88 or any claim dependent thereon is merely an obvious variation of any claim of the '344 patent. Indeed, the Examiner explicitly concedes that none of the claims of the '344 patent recites the specific polypeptide sequence set forth in SEQ ID NO:56. For at least these reasons, Applicants submit that the rejection is wholly improper and respectfully request that it be withdrawn.

Claims 88-95 and 102 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over "claims 1-19 of Rasmussen et al. (U.S. Patent No. 7, 14,574) in view of Pedersen et al .(U.S. Patent No. 6,531,122)". Office Action, page 6. Specifically, the Examiner contends that:

> Rasmussen et al. (U.S. Patent No. 7, 14,574) disclose IFN-β variants exhibiting IFN-β activity, comprising a variant sequence, which differs from the wild type human IFN-β sequence SEQ ID NO:2 in no more than 8 amino acid residues. However, the claims do not specifically recite IFN-β variant of SEQ ID NO:56 that has the following amino acids changed in SEQ ID NO:2 (C17S,Q49N, Q51N, D100F [sic], F111N and R113T). The claims also do not recite the molecular weight of PEG.

> Pedersen et al. (U.S. Patent No. 6,531,122) disclose PEGylation (see columns 13-26). Therefore, it would have been *prima facie* obvious at the time of the invention to generate PEGylated IFN-β variants with specific amino acid changes because Pedersen et al. reference discloses covalent attachment of PEG molecules to produce PEGylated interferons. One of ordinary skill in the art would have been motivated to generate PEGylated proteins because of the stability of the protein. Thus, IFN-β variant of SEQ ID NO:56 is an obvious embodiment of Rasmussen et al. Therefore, the instant invention is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of Rasmussen et al. (U.S. Patent No. 7, 14,574) in view of Pedersen et al (U.S. Patent No. 6,531,122).

Id. at page 6.

This rejection is respectfully traversed in part and overcome in part. Notably, the Examiner does not properly identify the patent number that serves as the basis for this rejection. Applicants assume that the Examiner is referring to U.S. Patent No. 7,144,574 (the '574 patent).

Applicants respectfully submit that the Examiner has not properly *prima facie* established by sufficient evidence that each of claims 88-95 and 102 represents an obvious variation over any of claims 1-19 of the '574 patent in view of the '122 patent. For example, the Examiner does not provide any specific reason why any of pending claims 88, 89, 94, and 95 would be deemed by one of ordinary skill in the art to constitute an obvious variation over any of claims 1-19 of the '574 patent. The Examiner does appear to assert that pending claims 91-93 would represent obvious variations over claims 1-19 of the '574 patent in view of the disclosure relating to pegylation at Columns 13-26 of the '122 patent. However, the Examiner does not point to any explicit disclosure in the '122 patent that would suggest the specific pegylated polypeptide as defined by claim 92, wherein the PEG molecule has a molecular weight of about 12 kDa, or the specific pegylated polypeptide as defined by claim 93, wherein the PEG molecule has a molecular weight of about 20 kDa.

Nor does the Examiner provide any explicit reason why pending claim 102 would be deemed by one of skill to be an obvious variation over any of claims 1-19 of the '574 patent in view of the '122 patent disclosure. Pending claim 102, which depends from claim 100, specifies a particular method of making a pegylated polypeptide. The Examiner does not provide any explicit evidence as to why the specific method of making a pegylated polypeptide defined by claim 102 would constitute an obvious variation over any of claims 1-19 of the '574 patent. For

at least these reasons, Applicants respectfully submit that a proper *prima facie* case of obviousness-type double patenting of claims 88-95 and 102 over the claims of the '574 patent in view of the '122 patent has not been established.

Nevertheless, in an effort to expedite prosecution, this rejection has been overcome by the enclosed terminal disclaimer of the '574 patent. Withdrawal of the rejection is respectfully requested.

Claims 96-101 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 85, 87, 93, 96, 97, 99, 100, and 102-108 of copending Application No. 10/351,189. Office Action, page 7. The Examiner finds that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention are also directed to [a] method of producing variant IFN-β with up to 9 [sic] amino acid changes to wild-type human IFN-β of SEQ ID NO:2." *Id.* The Examiner states that this rejection is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. *Id.*

This rejection is respectfully traversed. Claims 96-101 of the instant application all ultimately depend from claim 88. Claim 88 specifies a recombinant polypeptide comprising the polypeptide sequence of SEQ ID NO:56. As discussed above, the sequence set forth in SEQ ID NO:56 comprises the following six amino acid substitutions relative to the human IFN-β sequence shown in SEQ ID NO:2 – C17S+Q49N+Q51T+D110F+F111N+R113T.

Claims 85 of USSN 10/351,189 specifies an isolated nucleic acid comprising a nucleotide sequence encoding an interferon β polypeptide variant exhibiting an interferon β activity, the variant comprising a variant sequence which differs from the wild-type human interferon β sequence SEQ ID NO:2 in no more than 8 amino acid residues and which comprises at least one introduced N-glycosylation site selected from the group consisting of S2N+N4T/S, L9N+R11T/S, R11N, S12N+N14T/S, F15N+C16S/T, Q16N+Q18T/S, K19N+L21T/S, Q23N+H25T/S, G26N+L28T/S, R27N+E29T/S, L28N+Y30T/S, D39T/S, K45N+L47T/S, Q46N+Q48T/S, Q48N+F50T/S, Q49N+Q51T/S, Q51N+E53T/S, R71N+D73T/S, Q72N, D73N, S75N, S76N+G78T/S, L88T/S, Y92T/S, H93N+I95T/S, L98T/S, E103N+K105T/S,

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E104N+L106T/S, E107N+E109T/S, K108N+D110T/S, D110N, F111N+R113T/S, and L116N relative to SEQ ID NO:2.

Claim 85 of USSN 10/351,189 clearly does not recite or suggest a nucleic acid comprising a nucleotide sequence encoding the particular polypeptide comprising the sequence set forth in SEQ ID NO:56, as specified by claim 96 of the instant application. Claims 87, 93, 96, 97, 99, 100, and 102-108 of USSN 10/351,189 all ultimately depend from claim 85 and similarly do not disclose or suggest the subject matter of any of claims 96-101 of the instant application. For example, none of these claims of USSN 10/351,189 discloses or suggests a nucleic acid encoding the polypeptide comprising the sequence of SEQ ID NO:56, an expression vector comprising a nucleic acid encoding the polypeptide comprising the sequence of SEQ ID NO:56, a host cell comprising an expression vector comprising a nucleic acid encoding the polypeptide comprising the sequence of SEQ ID NO:56, or a method of making a polypeptide comprising the sequence of SEQ ID NO:56. For at least these reasons, Applicants submit that the rejection is improper. Withdrawal of the rejection is respectfully requested.

FEES

With entry of this Amendment, a total of 34 claims are pending (1 independent claim and 36 dependent claims). Applicants previously paid for a total of 34 claims and therefore believe that no additional claim fees are due.

Enclosed herewith is a Petition for Extension of Time Under 37 CFR 1.136(a) to extend the time for response for three months; the Commissioner is authorized to deduct $1050.00 from the undersigned's Deposit Account No. 50-0990 for this petition.

Also enclosed is a Terminal Disclaimer; the Commissioner is authorized to deduct the terminal disclaimer fee under 37 CFR 1.20(d) of $130.00 from the undersigned's Deposit Account No. 50-0990.

Also enclosed is a Petition to Correct Inventorship Pursuant to 37 C.F.R. § 1.48(b); the Commissioner is authorized to deduct $130.00 from the undersigned's Deposit Account No. 50-0990 for this Petition.

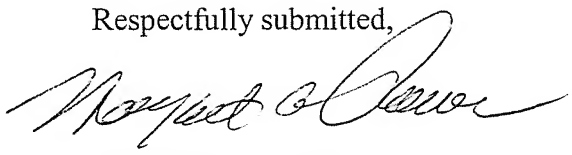
A Request for Corrected Filing Receipt is also enclosed herewith. It is believed that no fees are due for this Request.

In summary, it is believed that total fees in the amount of $1310.00 are due. The Commissioner is authorized to deduct this amount, or any fees required for this application, from the undersigned's Deposit Account No. 50-0990. Please also credit any overpayment to Deposit Account No. 50-0990.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5809.

Respectfully submitted,



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